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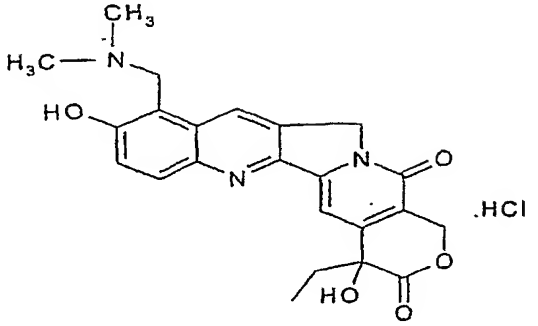
(54) Title: NOVEL CRYSTALLINE FORMS



(I)

(57) Abstract: The invention relates to a novel crystalline form of topotecan hydrochloride, and methods of making the same. The characteristic XRPD pattern and FT-IT patterns are shown in Figs. 1 and 2.

WO 2007/042799 A1

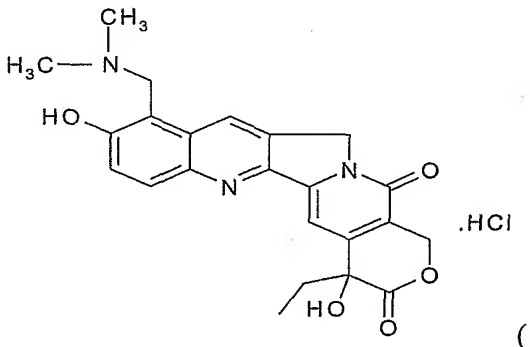
NOVEL CRYSTALLINE FORMS

Technical field:

The present invention relates to a novel crystalline polymorphic form of 10-[(dimethylamino) methyl]- 4-ethyl 4,9dihydroxy-1H-pyrano [3',4':6,7] indolizino [1,2-b] quinoline-3, 14 (4H, 12H) dione hydrochloride (topotecan hydrochloride) and the process for the synthesis of the same.

Background of the invention:

Topotecan hydrochloride is (10-[(dimethyl amino) methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano [3', 4' : 6, 7] indolizino[1, 2-b] quinoline-3, 14 (4H, 12H) dione hydrochloride) a compound of formula (I) .



(I)

Topotecan is a semi-synthetic analogue of camptothecin, an agent derived from the Oriental yew tree, Camptothecan accuminata. The cytotoxic effects of the camptothecins are believed to be related to their activity as inhibitors of topoisomerase – I, an enzyme involved in the replication and repair of nuclear DNA. As DNA is replicated in dividing cells, topoisomerase-I acts by binding to super-coiled DNA and causing single-stranded breaks in that DNA. As a result, topoisomerase –I is able to relieve the torsional stresses that are introduced into DNA ahead of the replication complex or moving replication fork. Topotecan inhibits topoisomerase-I by

stabilizing the covalent complex of enzyme and strand-cleaved DNA, which is an intermediate of the catalytic mechanism, thereby inducing breaks in the protein-associated DNA single-strands, resulting in cell death. Topotecan hydrochloride stops the growth of cancer cells by preventing the development of elements necessary for cell division.

US 5,004,758 discloses water soluble Camptothecin analogs, which includes topotecan (9-dimethylamino methyl-10- hydroxy camptothecin), preferably (S) –topotecan and its Hydrochloride salt.

US 5,734,056 disclose Camptothecin analogs (which include topotecan) and a process for the preparation of such analogs and its intermediates.

US 5,155,225 describes processes for making Pyrano [3',4':6,7]indolizino-[1,2-B] quinolinones.

WO2005046608 discloses a novel crystalline form of topotecan monohydrochloride pentahydrate, corresponding pharmaceutical compositions, methods of preparation and use for anti-viral and other cancer – related diseases.

The present invention relates to the solid state physical properties of topotecan hydrochloride. These properties can be influenced by controlling the conditions under which topotecan hydrochloride is obtained in solid form. Solid state physical properties include, for example, the flowability of the milled solid. Flowability affects the ease with which the material is handled during processing into a pharmaceutical product.

Another important solid state property of a pharmaceutical compound is its rate of dissolution in aqueous fluid. The rate of dissolution of an active ingredient in a patient's body fluid can have therapeutic consequences since it imposes an upper limit on the rate at which an orally-administered active ingredient can reach the patient's bloodstream.

Topotecan Hydrochloride exhibits polymorphism. Polymorphism is the property of some molecules to adopt more than one crystalline form in the solid state. A single molecule can give rise to a variety of crystalline solids having distinct physical properties that can be measured in a laboratory like its thermal behaviour, e.g. melting point and differential scanning calorimetry (DSC) thermogram, dissolution rate, flowability, X-ray diffraction pattern, infrared absorption spectrum and NMR spectrum.

The differences in the physical properties of polymorphs result from the conformation, orientation and intermolecular interactions of adjacent molecules in the crystalline solid. Rate of dissolution of a pharmaceutical compound depends upon its stable crystalline form. The rate of dissolution can have increased effect on the therapeutic efficacy of the administered drug. Hence, this property of the pharmaceutical compound is considered as an important feature in formulating syrups, elixirs and other liquid medicaments. The solid state form of a compound may also affect its behavior on compaction and its storage stability.

Thus, it is clear from the foregoing discussion, it would be desirable to have active pharmaceutical ingredient in a stable crystalline form having improved bulk handling and dissolution properties and this becomes the object of the present invention

Object of the Invention:

An object of the present invention is to provide a novel crystalline polymorphic form of topotecan hydrochloride hereinafter referred to as Form-A.

Another object of the present invention is to provide a process for preparing the novel crystalline polymorphic Form-A of topotecan hydrochloride from any crystalline form of topotecan Hydrochloride, pentahydrate or amorphous.

Yet another object of the present invention is to provide a process for the preparation of novel crystalline polymorphic Form-A of topotecan hydrochloride from topotecan base.

Summary of the invention:

The present invention relates to a novel polymorphic form of topotecan hydrochloride which is hereinafter designated as form A.

According to one aspect of the invention there is provided a crystalline form A of topotecan hydrochloride having an XRPD pattern with peaks at 6.08, 6.94, 8.10, 9.96, 10.16, 11.68, 12.28, 13.08, 13.62, 14.32, 15.44, 16.46, 16.56, 17.58, 18.42, 19.32; 20.14, 21.22, 21.88, 22.54, 22.72, 23.38, 24.14, 24.36, 24.78, 25.02, 25.50, 26.42, 26.86, 27.18, 27.44, 28.10, 28.76, 29.42, 29.68 and 30.02 °2θ (± 0.2°).

According to one aspect of the invention there is provided a crystalline form A of topotecan hydrochloride having characteristic FT-IR peaks at 1743 , 1656 , 1596 , 1560 and 1507 cm^{-1}.

According to one aspect of the invention there is provided a crystalline form A of topotecan hydrochloride having an XRPD pattern as shown in Figure 1.

According to one aspect of the invention there is provided a crystalline form A of topotecan hydrochloride having an FT-IR spectrum as shown in Figure 2.

In another aspect, there is provided a process of converting topotecan hydrochloride of any crystalline form, anhydrous, pentahydrate, or amorphous form into the novel crystalline topotecan hydrochloride Form A.

In a further aspect there is provided a process for preparation of topotecan hydrochloride form A from topotecan base by dissolving the latter in suitable organic solvent.

The compound of the present invention, topotecan hydrochloride form A can be formulated into a variety of compositions for administration to humans and mammals. Dosage forms include

solid dosage forms like tablets, powders, capsules, sachets, troches and lozenges as well as liquid syrups, suspensions and elixirs. The active ingredient (s) and excipients can be formulated into compositions and dosage forms according to methods known in the art.

According to another aspect of the invention there is provided a process for preparing crystalline form A of topotecan hydrochloride, comprising: suspending topotecan hydrochloride in methanol; stirring at a temperature ranging from 25 to 30°C; cooling the reaction mass to -10 to 25°C, preferably while stirring it; and recovering the topotecan hydrochloride Form A preferably by filtration and drying. The topotecan hydrochloride used to form the topotecan hydrochloride Form A may be formed by convention means. It may be crystalline or amorphous. It may be anhydrous or in the form of the pentahydrate.

According to another aspect of the invention there is provided a process for preparing crystalline form A of topotecan hydrochloride, comprises suspending topotecan base in methanol; adding aqueous HCl and stirring at 25-30°C; cooling the reaction mass to a temperature ranging from -10 to 25°C, preferably while stirring it; and recovering the topotecan hydrochloride Form A preferably by filtration and drying.

The reaction mass is preferably stirred for about one hour while at 25-30°C. The cooling preferably is carried out over about one hour. The filtration is preferably carried out over about 4-6 hours, e.g.5 hours, while the filtration is preferably carried out over 30 to 40 hours, e.g. 36 hours.

Brief Description of the Drawings

The invention is illustrated by reference to the accompanying drawings described below

Figure 1 shows powder X-ray diffractogram of the Form 'A' crystalline polymorph of topotecan hydrochloride.

Figure 2 shows FT-IR (KBr) spectrum of the Form 'A' crystalline polymorph of topotecan hydrochloride.

Detailed Description of the Invention

The present invention relates to a novel polymorphic form of topotecan hydrochloride which is hereinafter designated as form A. In one aspect the present invention provides a novel crystalline polymorphic Form-A of topotecan hydrochloride which is characterized by an XRD pattern (Figure1) having peak positions at 6.08, 6.94, 8.10, 9.96, 10.16, 11.68, 12.28, 13.08, 13.62, 14.32, 15.44, 16.46, 16.56, 17.58, 18.42, 19.32; 20.14, 21.22, 21.88, 22.54, 22.72, 23.38, 24.14, 24.36, 24.78, 25.02, 25.50, 26.42, 26.86, 27.18, 27.44, 28.10, 28.76, 29.42, 29.68 and 30.02 °2θ (± 0.2°).

The present invention also provides a novel crystalline polymorphic Form A of topotecan hydrochloride characterized by FT-IR (KBr) spectrum as depicted in figure 2. Form A provides an infrared spectrum containing peaks at 1743, 1656, 1596, 1560 and 1507.

In another aspect the present invention provides a process of preparing a novel crystalline polymorphic Form-A of topotecan hydrochloride which comprises suspending topotecan base in a suitable solvent preferably methanol and adding aqueous HCl and stirring at 25-30°C and further cooling it, preferably while stirring, to at a temperature ranging from –10 to 25°C preferably at 10-15°C and filtering the solid, and drying, preferably at 25 – 30°C under vacuum to obtain uniform crystals of topotecan hydrochloride Form A. The stirring of the reaction mass at 25-30°C is preferably carried out for about 1 hour.

In another aspect the present invention provides a process of converting topotecan hydrochloride of any crystalline form, anhydrous, pentahydrate, or amorphous form into the novel crystalline topotecan hydrochloride Form A which comprises suspending topotecan hydrochloride in a suitable solvent preferably methanol and stirring at a temperature ranging from –10 to 25°C preferably at 10-15°C, filtering the solid, and drying at 25 – 30°C under vacuum followed by drying, preferably at 30 - 35° C, for about 36 hours to obtain uniform crystals of topotecan hydrochloride Form A.

The topotecan hydrochloride Form A of this invention has a water content in the range of 10 to 12%.

The novel crystalline polymorphic form A of topotecan hydrochloride is readily isolated, and displays uniformity, reproducibility, ease and safety of handling in manufacture and stability on isolation and drying.

The topotecan hydrochloride form A is preferably provided in the form of the (4S)- isomer. The purity of the isomer may be up to about 99.5%.

The topotecan hydrochloride according to the invention may be combined with a pharmaceutically acceptable carrier to form suitable pharmaceutical compositions. It may be used in therapy such as in a method of treating tumours.

According to another aspect of the invention there is provided the crystalline form A of topotecan hydrochloride as described above for use in therapy.

According to another aspect of the invention there is provided the crystalline form A of topotecan hydrochloride as described above for use in the treatment of a tumour.

According to another aspect of the invention there is provided the crystalline form A of topotecan hydrochloride as described above for use in the manufacture of a medicament for the treatment of a tumour.

According to another aspect of the invention there is provided a method of treating a tumour comprising administering a therapeutically effective amount of a crystalline form A of topotecan hydrochloride as described above, to a patient in need thereof. A typical dosage would be about 4 mg, suitably provided in an injection formulation.

The nature of the invention, its object and advantages are explained hereunder in greater detail in relation to non-limiting exemplary embodiments.

Example 1

Preparation of topotecan hydrochloride (Form A)

10 grams of topotecan hydrochloride amorphous form was suspended in 100 ml of Methanol at 25-30°C. The mixture was stirred for 1 hour at 25-30°C and further chilled to 10 - 15° C and stirred for additional 1 hour at 10 - 15° C and filtered; the solid was washed with 5 ml of methanol. The resulting product was dried under vacuum at 25 - 30° C for 5 hours, followed by drying at 30 - 35° C for 36 hours to give 9.0 g of topotecan hydrochloride Form 'A'.

Example 2

Preparation of topotecan hydrochloride (Form A)

10.0 g of topotecan hydrochloride pentahydrate was suspended in 100 ml of methanol and stirred at 25-30°C for 1 hour and further chilled to 10 - 15° C and stirred for 1 hour at 10 - 15° C. The resulting solid was filtered and washed with 5 ml of methanol. The solid was dried in vacuum at 25 - 30° C for 5 hours, followed by drying at 30 - 35° C for 36 hours to get 6.0 g of Form 'A'.

Example 3

Preparation of topotecan hydrochloride (Form A)

10 grams of topotecan base was suspended in 100 ml Methanol, and 2.4 ml HCl was added at 25-30°C and stirred for 1 hour at 25-30°C, the suspension was further chilled to 10 - 15° C and stirred for 1 hour at 10 - 15° C and filtered, washed with 5 ml of methanol. The product was dried in vacuum at 25 - 30° C for 5 hours, followed by drying at 30 - 35° C for 36 hours to get 8.0 g of topotecan hydrochloride Form 'A'.

CLAIMS:

1. A crystalline form A of topotecan hydrochloride having an XRPD pattern with peaks at 6.08, 6.94, 8.10, 9.96, 10.16, 11.68, 12.28, 13.08, 13.62, 14.32, 15.44, 16.46, 16.56, 17.58, 18.42, 19.32; 20.14, 21.22, 21.88, 22.54, 22.72, 23.38, 24.14, 24.36, 24.78, 25.02, 25.50, 26.42, 26.86, 27.18, 27.44, 28.10, 28.76, 29.42, 29.68 and 30.02 °2θ (± 0.2°).

2. A crystalline form A of topotecan hydrochloride having characteristic FT-IR peaks at 1743 , 1656 , 1596 , 1560 and 1507 cm^{-1}.

3. A crystalline form A of topotecan hydrochloride according to Claim 1 or 2, wherein the Topotecan hydrochloride has a water content in the range of about 10 to 12 wt%.

4. A crystalline form A of topotecan hydrochloride having an XRPD pattern as shown in Figure 1.

5. A crystalline form A of topotecan hydrochloride having an FT-IR spectrum as shown in Figure 2.

6. A crystalline form of topotecan hydrochloride having a water content in the range of about 10 to 12 wt%.

7. A crystalline form A of topotecan hydrochloride according to any preceding claim, comprising (4S)-topotecan hydrochloride.

8. A process for preparing crystalline form A of topotecan hydrochloride, comprising: suspending topotecan hydrochloride in methanol; stirring at a temperature ranging from 25 to 30°C; cooling the reaction mass to -10 to 25°C; and recovering the topotecan hydrochloride Form A by filtration and drying.

9. A process for preparing crystalline form A of topotecan hydrochloride, comprises suspending topotecan base in methanol; adding aqueous HCl and stirring at 25-30°C; cooling the reaction mass to a temperature ranging from -10 to 25°C; and recovering the topotecan hydrochloride Form A by filtration and drying.

10. A process according to claim 8 or 9, wherein the reaction mass is cooled to a temperature ranging from 10 to 15 °C.

11. A process according to claim 8, 9 or 10, wherein the reaction mass is stirred during said cooling step.

12. A crystalline form A of topotecan hydrochloride obtaining by a process according to any one of claims 8 to 11.

13. A pharmaceutical formulation comprising a crystalline form A of topotecan hydrochloride according to any one of claims 1 to 7, or according to claim 12, in combination with a pharmaceutically acceptable carrier.

14. A crystalline form A of topotecan hydrochloride according to any one of claims 1 to 7, or according to claim 1, for use in therapy.

15. A crystalline form A of topotecan hydrochloride according to any one of claims 1 to 7, or according to claim 12, for use in the treatment of a tumour.

16. A crystalline form A of topotecan hydrochloride according to any one of claims 1 to 7, or according to claim 12, for use in the manufacture of a medicament for the treatment of a tumour.

17. A method of treating a tumour comprising administering a therapeutically effective amount of a crystalline form A of topotecan hydrochloride according to any one of claims 1 to 7 or 12, to a patient in need thereof.

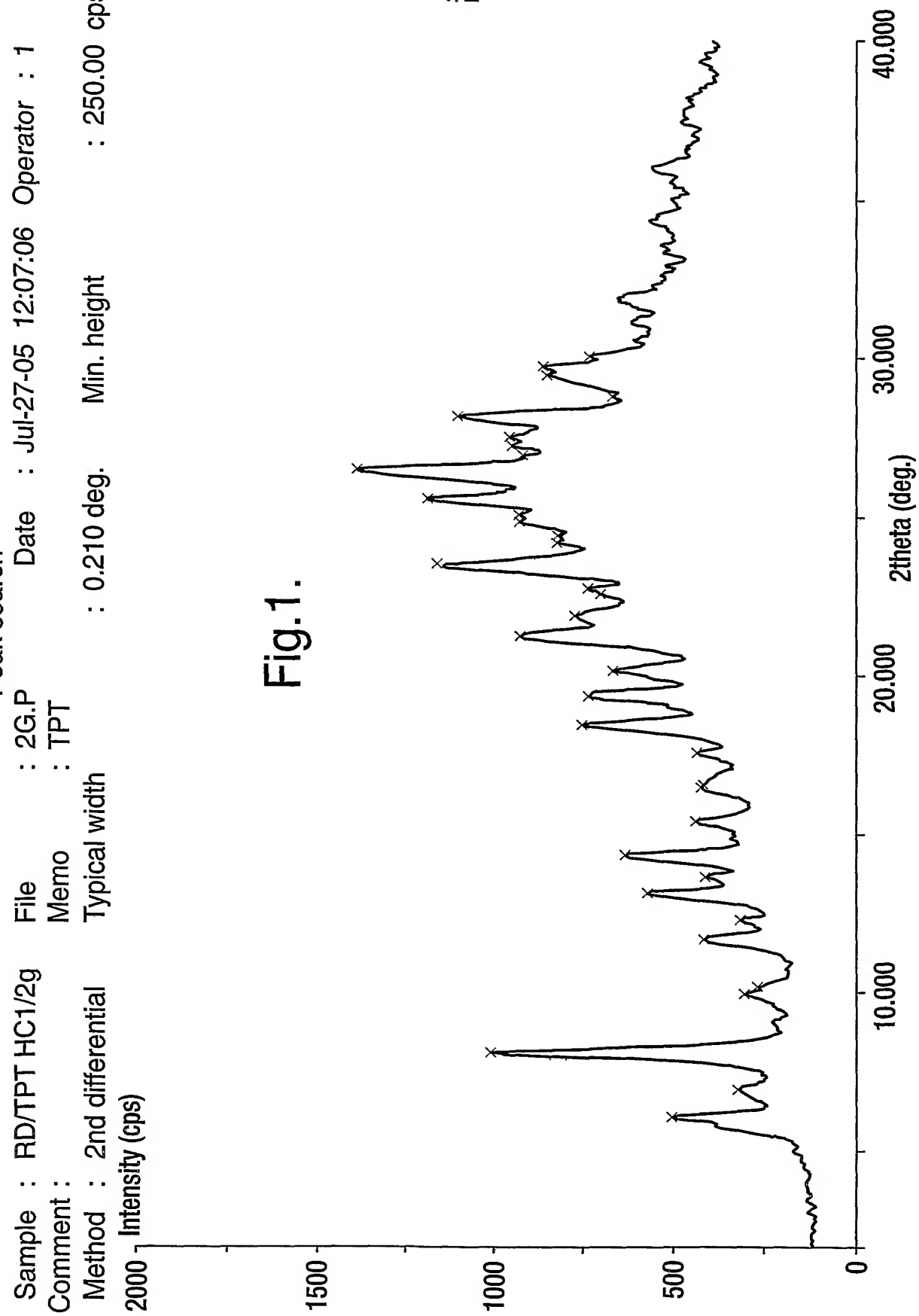

Peak search
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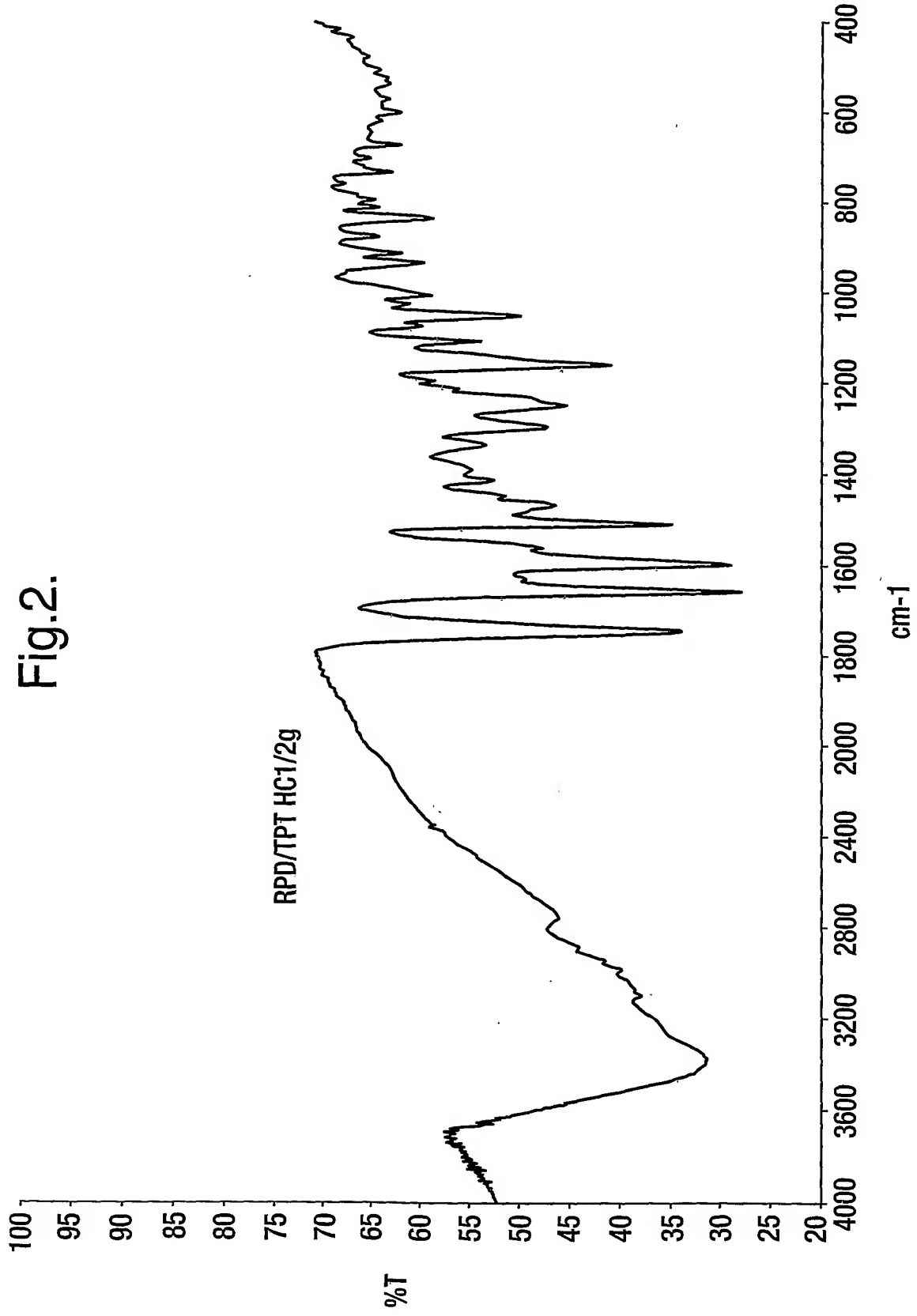
Fig.1.

Fig.2.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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/003768

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/22 A61K31/4745 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEN M. ET AL: "Studies on the polymorph of topotecan hydrochloride and its stability" CHINESE JOURNAL OF BIOCHEMICAL PHARMACEUTICS, vol. 26, no. 5, 2005, pages 279-281, XP001248432 abstract	1-12
A	WO 2005/046608 A2 (SMITHKLINE BEECHAM CORP [US]; DELL ORCO PHILIP C [US]; DIEDERICH ANN M) 26 May 2005 (2005-05-26) cited in the application the claims	1-17

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2007	05/02/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bakboord, Joan

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/003768

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	VOGT ET AL: "A study of variable hydration states in topotecan hydrochloride" JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS, NEW YORK, NY, US, vol. 40, no. 5, 18 March 2006 (2006-03-18), pages 1080-1088, XP005296966 ISSN: 0731-7085 the whole document	1-12

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2006/003768

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 17
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 17 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2006/003768

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005046608 A2	26-05-2005	AU 2004289318 A1	26-05-2005
		CA 2545876 A1	26-05-2005
		EP 1689400 A2	16-08-2006